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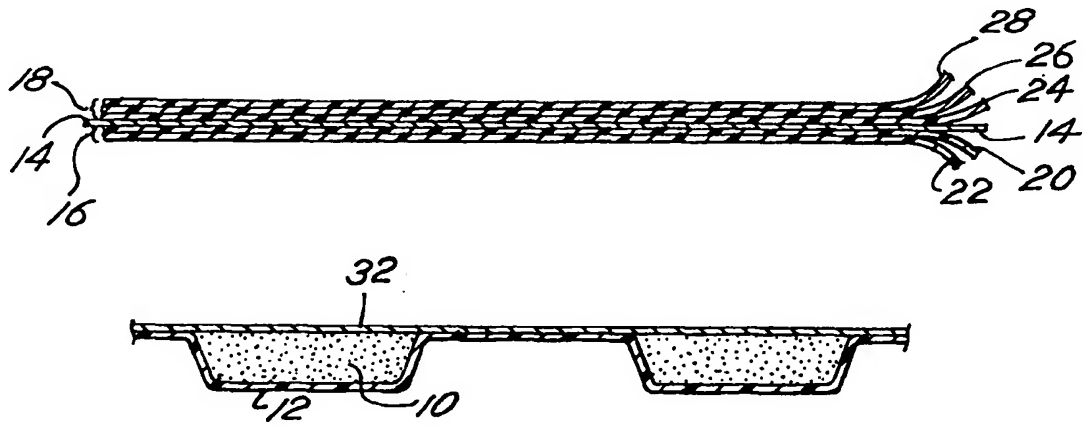
(54) Title: IMPROVED METHOD FOR MANUFACTURING FREEZE DRIED DOSAGES IN A MULTILAMINATE BLISTER PACK



(57) Abstract

An improved method for manufacturing freeze dried pharmaceutical tablets in blister packs is disclosed. Liquid dosages are introduced into a multilayer laminated blister sheet having an impermeable intermediate layer (14) that is positioned between first and second outer layers (16, 18) each of which has substantially the same coefficient of thermal expansion. The properties of the outer layers of the blister sheet are such that there are no inter-layer stresses that will cause curvature of the blister sheet when it is subjected to temperature changes during the freezing and freeze drying steps. Following the introduction of the dosages into the depressions (10) of the blister sheet, the dosages are frozen and freeze dried. A lidding sheet (32) is then attached to the blister sheet to seal the solid dosages into the blister pack.

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IMPROVED METHOD FOR MANUFACTURING FREEZE DRIED DOSAGES IN A MULTILAMINATE BLISTER PACK

BACKGROUND OF THE INVENTION

This invention relates generally to the field of manufacturing and dispensing pharmaceuticals, and more particularly to an improved method for manufacturing freeze dried pharmaceutical tablets in disposable single dose aluminum blister packs. In recent years, pharmaceutical producers have turned to the use of blister packs for use in both the forming and dispensing of pharmaceutical tablets. These blister packs generally consist of a blister sheet or blister film and a lidding sheet. The blister sheet contains depressions for containing individual dosages. In a standard process for manufacturing freeze dried tablets, a single dosage, in liquid form, is introduced into each depression of the blister sheet. The blister sheet, along with the liquid dosages, is then placed into a refrigerated environment where the dosages are subjected to low temperatures to freeze them. The blister sheets are then transferred to a freeze drier, where the ice is removed by sublimation. When freeze drying is completed, the sheets are removed from the drying chamber and covered with an adhesive lidding sheet, which seals the solid dosages into their individual depressions. United States Patent No. 4,305,502 is incorporated herein by reference as teaching, inter alia, a known process for manufacturing freeze dried tablets.

However, blister sheets that have heretofore been used in freezing and freeze drying processes have suffered from several deficiencies. First, the blister sheets have typically been made of a polymeric substance, which, over time, can allow moisture to permeate the blister pack and reach the dosages stored inside. To solve this problem, blister sheets have been developed in which a layer of aluminum is laminated between layers of polymer. While the presence of the aluminum layer prevents moisture from permeating the blister pack, it leads to a second problem. Namely, when subjected to temperature changes during the freezing process, conventional aluminum/polymer laminates tend to curl up, due to the differences in the degree of thermal expansion or contraction of the opposing layers of the laminate. This makes their use in freezing processes difficult, since liquid product can easily spill from the formed depressions or can lie unevenly in the depressions during filling and freezing operations. Furthermore, the curling of the blister sheet can cause dosages to freeze or sublimate unevenly, since some depressions may not be in physical contact with the cold surfaces of the refrigerator or freeze drier. The only solution has been

to use weights on the edges of the laminate strips to hold them sufficiently flat. Such measures are not practical in large scale manufacturing operations, and can interfere with the freezing process.

A need therefore exists for a method of utilizing a high barrier aluminum laminate in the manufacture of freeze dried dosage forms that avoids the problem of curling of the blister sheet.

SUMMARY OF THE INVENTION

In a basic aspect, the invention is an improved method for manufacturing freeze dried dosage forms in aluminum blister packs. The dosages are introduced as a liquid into the depressions of a blister sheet. The blister sheet comprises an impermeable intermediate layer positioned between first and second outer layers, with each of the outer layers having substantially the same overall coefficient of thermal expansion, as that term is defined herein. The properties of the outer layers of the laminate are such that there are no inter-layer stresses that will cause curvature of the laminate when it is subjected to temperature changes during the freeze drying process. The symmetrical response of the outer layers to such temperature changes can be achieved by using the same film material for both outer layers, or by using different materials which, by virtue of their intrinsic properties or thickness, exhibit similar degrees of thermal expansion or contraction. The outer layers can each consist of separate sublayers, as long as the sublayers in one outer layer are such that the outer layer, as a whole, exhibits the same overall degree of expansion or contraction as the other outer layer. Following the introduction of the dosages into the depressions of the blister sheet, the dosages are frozen and freeze dried. A lidding sheet is then attached to the blister sheet to seal the solid dosages into the blister pack.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 of the drawing is a plan view of a blister sheet, showing the configuration of the dosage depressions;

Figure 2 of the drawing is a transverse cross sectional view of said blister pack, taken generally along the line 2--2;

Figure 3 of the drawing is a cross sectional view of a blister sheet illustrating in further detail the relationship between the intermediate and outer layers of the blister sheet;

Figure 4 of the drawing is a cross sectional view of a blister sheet illustrating in further detail the relationship between the various layers and sublayers of the blister sheet;

Figure 5 of the drawing is a cross sectional view of a blister pack with the lidding sheet in place.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As discussed above, the invention is an improved method for manufacturing freeze dried dosage forms in aluminum blister laminates. Turning to Figure 1 and Figure 2, to form the blister pack, depressions 10 are formed in a strip 12 of the desired laminate through conventional cold forming. The size and shape of the depressions is a matter of choice that will be dictated by the size and nature of the tablet to be formed, as well as other considerations that are well known to those persons skilled in the art.

Turning to Figure 3, the laminate strip 12 comprises an intermediate layer 14 that is substantially impermeable to moisture. The preferred material for the intermediate layer is aluminum having a thickness of 10 to 100 μm, with the preferred thickness being approximately 45μm, although other suitable materials may be used in its place. The intermediate aluminum layer 14 is sandwiched between a first outer layer 16 and a second outer layer 18. The outer layers may be coated or laminated onto the intermediate layer, but the layers do not necessarily have to be bonded together. The first and second outer layers are preferably made of polymeric substances, including polyamide, polyvinylchloride, polypropylene or other such substances. The first and second outer layers can be made of the same or different materials, and may have different thicknesses, as long as they have substantially similar coefficients of thermal expansion, i.e., are made of such materials and have such thickness that the first and second outer layers exhibit substantially the same degree of expansion or contraction within the plane of the film when the laminate is subjected to changes in temperature, particularly within the range of temperatures encountered during the freezing process, in which temperatures can be as low as -196°C. For instance, the laminated film 12 can consist of an intermediate layer 14 of aluminum, positioned between first and second outer layers of polypropylene 16 and 18, each layer being approximately 50 μm thick.

Turning to Figure 4, it can be seen that one or both of the outer layers can also consist of separate sublayers, with each sublayer being either polymeric or nonpolymeric. For instance, the first outer layer 16 can consist of two or more sublayers, such as a polyamide sublayer 20 and a polyvinylchloride sublayer 22. The second outer layer 18 can consist of a identical sublayers, or can also consist of two or more sublayers, illustrated as 24, 26 and 28, that are different than the

sublayers in the first outer layer 16. Materials that may be used as sublayers include the above mentioned polymers, as well as lacquer, aluminum or paper. A priming layer can also be included. Again, the primary concern is that the first outer layer 16 and the second outer layer 18 exhibit, overall, substantially the same degree of expansion or contraction in response to temperature changes, so as to prevent curling of the blister sheet.

Returning to Figure 1, a single dosage 30 of pharmaceutical, in liquid form, is introduced into each depression in the blister sheet in a conventional manner. The blister sheet is then placed into a refrigeration unit, for instance a nitrogen spray freezing chamber, where both the sheet and the dosages are subjected to temperatures sufficient to rapidly freeze the dosages, typically as low as -196°C. Once the dosages have frozen, the blister sheet is transferred to a freeze drying chamber. Within the freeze drying chamber, the dosages are subjected to a vacuum of typically 0.1 to 1.0 mBar for a period of 180 to 500 minutes. At the same time, the temperature is steadily increased from typically about -30°C to about 60°C. As shown in Figure 5, once the dosages have been freeze dried, an adhesive lidding sheet 32 is positioned over the blister sheet, sealing the dosages into the individual depressions of the blister sheet. The procedures associated with the introduction of dosages into the blister sheet, the freezing and freeze drying of the dosages and the attachment of the lidding sheet are known to persons of skill in the art, and need not be treated in great depth herein.

While in the foregoing there have been described preferred embodiments of the invention, it should be understood to those skilled in the art that various modifications and changes can be made without departing from the true spirit and scope of the invention

WHAT IS CLAIMED IS:

1. A method for manufacturing freeze dried dosage forms in a blister pack, the method comprising

a) introducing liquid dosages into the depressions of a multilayer laminated blister film, the film comprising first and second outer layers and an impermeable intermediate layer positioned between the first and second outer layers, the first and second outer layers having substantially similar coefficients of thermal expansion;

b) freezing the dosages;

c) freeze drying the dosages and

d) attaching a lidding sheet to the blister film to seal the dosages into the depressions of the blister film.

2. The method of claim 1, wherein the intermediate layer of the blister film is aluminum.

3. The method of claim 1, wherein the first and second outer layers of the blister film are made of the same substances.

4. The method of claim 1, wherein at least one of the outer layers of the blister film is a polymeric substance.

5. The method of claim 4, wherein the polymeric substance consists essentially of one or more polymers selected from the group consisting of polyethylene, polyamide, polyvinylchloride and polpropylene.

6. The method of claim 1, wherein the first and second outer layers of the blister film have substantially the same thickness.

7. The method of claim 1, wherein at least one of the outer layers of the blister film further comprises a plurality of sublayers.

8. The method of claim 7, wherein one of the sublayers is a lacquer or priming layer.

9. The method of claim 7, wherein one of the sublayers is a polymeric substance.

10. The method of claim 9, wherein the polymeric substance consists essentially of one or more polymers selected from the group consisting of polyethylene, polyamide, polyvinylchloride and polypropylene.

11. A method for manufacturing freeze dried dosage forms in a blister pack, the method comprising

a) introducing liquid dosages into depressions in a multilayer laminated blister film, the film comprising first and second polymeric outer layers having substantially similar coefficients of thermal expansion, and an aluminum intermediate layer positioned between the first and second layers and bonded thereto;

b) freezing the dosages;

c) freeze drying the dosages and

d) attaching a lidding sheet to the blister film to seal the dosages into the depressions of the blister film.

Fig.1

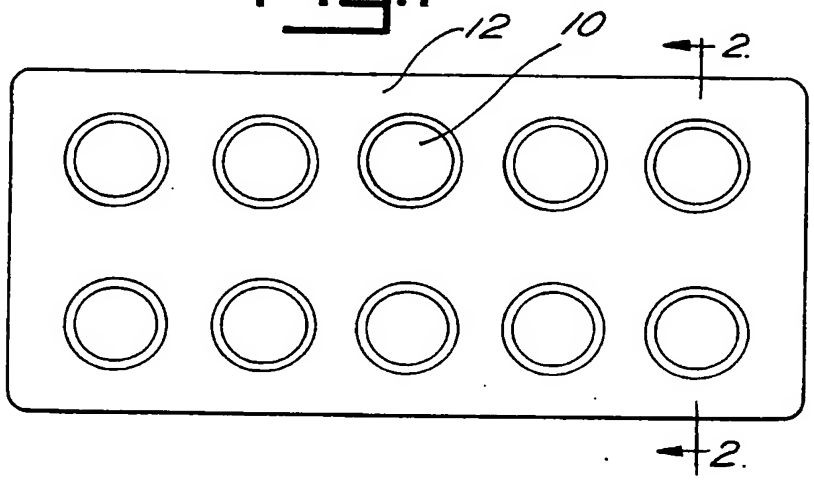


Fig.2

Fig.3

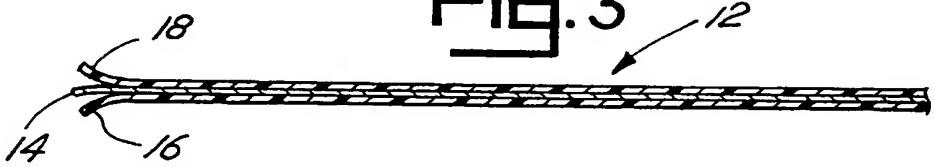


Fig.4

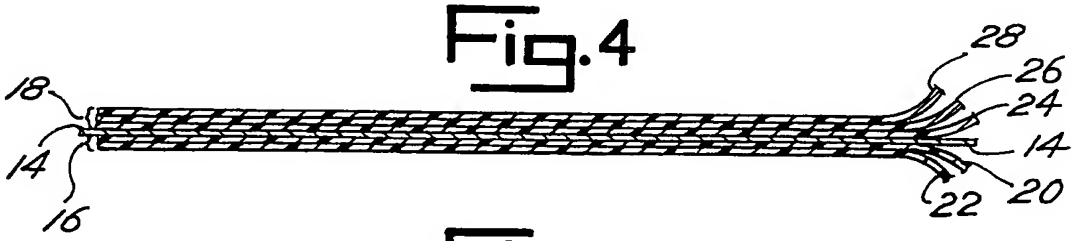
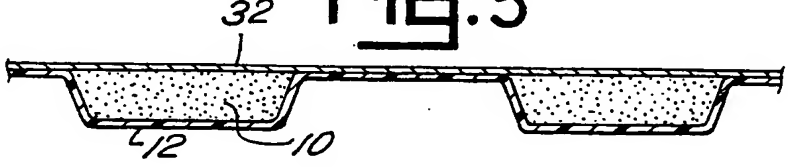


Fig.5



SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 93/02459

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61J1/00 B65D75/34 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61J B65D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 305 502 (GREGORY ET AL.) 15 December 1981 cited in the application see abstract see column 3, line 21 - column 4, line 16 see column 4, line 25 - line 55; claims 7-10; figures 1-3; example 1 ---	1-11
Y	US,A,4 150 744 (FENNIMORE) 24 April 1979 see column 1, line 5 - line 31 see column 1, line 50 - line 58 see column 2, line 53 - column 3, line 16; claim 1; figure 1 --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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7 February 1994	04.03.94
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 389 207 (MERCK & CO., INC.) 26 September 1990 see column 1, line 23 - line 49 see column 2, line 17 - column 2, line 45; figures 1-3	1-11
A	EP,A,0 286 407 (KUREHA KAGAKU KOGYO KK) 12 October 1988 see abstract see page 2, line 3 - line 37 see page 4, line 3 - line 10; claims 1,2,9,10; example 3	1-11
A	US,A,5 014 851 (WICK) 14 May 1991 see claims 4,15; figures 1,2	1,11

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
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